

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>C08L 3/08, 3/18, C09D 103/08, C08L 3/10, C09D 103/10, A61K 9/48, 9/50</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/18835</b> <b>(43) International Publication Date:</b> 6 April 2000 (06.04.00)
<b>(21) International Application Number:</b> PCT/US99/18139 <b>(22) International Filing Date:</b> 11 August 1999 (11.08.99) <b>(30) Priority Data:</b> 98/12246                      30 September 1998 (30.09.98)    FR 09/240,504                    29 January 1999 (29.01.99)        US <b>(71) Applicant:</b> WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). <b>(72) Inventors:</b> SCOTT, Robert, Anthony; Koninin Elisabethplein 26, Bus 4, B-9100 Sint-Niklaas (BE). CADE, Dominique; 11, rue du Jura, F-68280 Andolsheim (FR). HE, Xiongwei; 3, rue du Jura, F-68280 Andolsheim (FR). <b>(74) Agents:</b> RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.		<b>(81) Designated States:</b> AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> MODIFIED STARCH FILM COMPOSITIONS  <b>(57) Abstract</b>  <p>The invention concerns compositions from modified starches, such as starch ethers or oxidized starch, more particularly hydroxypropylated starch (HPS) or hydroxyethylated starch (HES) for the use in pharmaceutical, veterinary, food, cosmetic or other products like films for wrapping food, aspics or jellies, preferably for predosed formulations like soft or hard capsules. The hard capsules obtained by the present invention with a conventional dipping molding process are similar to hard gelatine capsules (HGC).</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

### Modified Starch Film Compositions

The invention concerns compositions from modified starches, such as starch ethers and oxidized starch, more particularly  
5 hydroxpropylated starch (HPS) and hydroxyethylated (HES) for the use in pharmaceutical, veterinary, food, cosmetic or other products like films for wrapping food, aspics or jellies, preferably for predosed formulations like soft or hard capsules. The hard capsules obtained by the present  
10 invention are similar to hard gelatine capsules (HGC).

A second embodiment of the invention is the use of the modified starch compositions for the manufacturing of hard capsules by conventional dip moulding process as normally used in the production of conventional hard gelatine  
15 capsules.

For the industrial manufacture of pharmaceutical capsules gelatine is most preferred for its gelling, film forming and surface active properties. The manufacture of hard gelatine capsules by dip moulding process exploits fully its gelling  
20 and film forming abilities. Such capsules are manufactured by dipping mould pins into a hot solution of gelatine, removing the pins from the gelatine solution, allowing the gelatine solution attached on pins to set by cooling, drying and stripping the so-formed shells from the pins. The setting of  
25 the solution on the mould pins after dipping is the critical step to obtain a uniform thickness of the capsule shell.

Attempts have been made to manufacture capsules with materials other than gelatine, notably with modified cellulose. Successful industrial examples are the capsules  
5 made of hydroxypropyl methylcellulose (HPMC). The HPMC capsules show several advantages over HGC. However, the raw material HPMC is significantly more expensive than gelatine.

Starch is another abundant natural polysaccharide which is renewable, biodegradable and of low cost. Because of the  
10 limited film forming ability and poor mechanical properties, the success in this field is more limited. A unique industrial example (US 4,738,724) are starch capsules produced by injection moulding, but such capsules have a much higher shell thickness and a different shape which requires  
15 specific filling and closing equipment.

US 4,026,986 describes the manufacture of HPS capsules by dip moulding process. However, due to the absence of setting ability of HPS solution, the dipping time is long (20 seconds), and therefore it did not result in commercial  
20 process.

Surprisingly, we found that the addition of a very small amount of a setting system, preferably consisting of hydrocolloids, most preferably polysaccharides, confers to HPS OR HES solution an appropriate setting ability with the  
25 result that hard HPS OR HES capsules can be manufactured by the dip moulding process of hard gelatine capsules under conventional process conditions.

The aim of the invention is therefore the provision of compositions based on HPS or HES for the use in pharmaceutical, veterinary, food, cosmetic or other products like films for wrapping food, aspics or jellies, preferably  
5 for containers for predosed formulations like soft or hard capsules and wherein the HPS or HES compositions have in aqueous solution a sufficient setting ability.

The first object of the invention is compositions based on HPS or HES to improve and adjust the mechanical properties of  
10 films for various applications.

We found that the addition of a plasticizer in the formulation can improve dramatically the HPS OR HES film flexibility. The plasticizer or mixture of plasticizers is selected from polyethylene glycol, glycerol, sorbitol,  
15 sucrose, corn syrup, fructose, dioctyl-sodium sulfosuccinate, triethyl citrate, tributyl citrate, 1,2-propylenglycol, mono-, di- or triacetates of glycerol, or natural gums. Preferred are glycerol, polyethylene glycol, propylene glycol, citrates and their combinations. The amount of plasticizer depends on  
20 the final application. For hard film formulations, such as for hard capsules, the plasticizer is contained in an amount of 0 to 20%, preferably 10-20%. A higher content, 20-30%, is preferred for soft film formulations, such as for soft capsules.

25 We found also that it is possible to further improve the film mechanical properties, by combining the HPS or HES with other hydrosoluble polymers or polysaccharides. The preferable

examples are pectin, alginates, polyvinyl alcohol and high molecular weight polyethylene glycol.

The second object of the present invention is the achievement of an adequate setting ability of the HPS OR HES solution for process purpose.

The addition of a setting system, preferably based on polysaccharides, to HPS OR HES solutions enables the adaptation of specific and desired gelling properties for a selected process (film forming or dip moulding such as the production of hard HPS OR HES capsules by a conventional dipping process). For the production of hard capsules by dip moulding process, it is extremely important that the film forming HPS OR HES solution remaining on the mould pins after dipping is prohibited from flowing down the pins. Otherwise the obtained film will not have the desired uniform thickness.

With the compositions of the present invention we can produce hard HPS OR HES capsules with the same equipment and in the same range of process conditions as used for the production of conventional hard gelatine capsules. Furthermore capsules produced from compositions of the instant invention have the same dimensional specifications and allow the use of the existing filling machinery and do not require specific and new equipment for the filling process.

The HPS OR HES concentration in the dipping solution is in a range of 10 to 50%, preferably in the range of 20 to 40% by weight.

The setting system consists of a hydrocolloid or mixtures of hydrocolloids and may contain in addition cations and/or sequestering agents.

Suitable hydrocolloids or mixtures producing synergistic properties may be selected from natural seaweeds, natural seed gums, natural plant exudates, natural fruit extracts, biosynthetic gums, gelatines, biosynthetic processed starch or cellulosic materials, preferred are polysaccharides.

The preferred polysaccharides are alginates, agar gum, guar gum, locust bean gum (carob), carrageenan, tara gum, gum arabic, ghatti gum, Khaya grandifolia gum, tragacanth gum, karaya gum, pectin, arabian (araban), xanthan, gellan, starch, Konjac mannan, galactomannan, funoran, and other exocellular polysaccharides. Preferred are exocellular polysaccharides.

The preferred exocellular polysaccharides are xanthan, acetan, gellan, welan, rhamsan, furcelleran, succinoglycan, scleroglycan, schizophyllan, tamarind gum, curdlan, pullulan, and dextran.

The preferred hydrocolloids are kappa-carrageenan or gellan gum or combinations like xanthan with locust bean gum or xanthan with konjac mannan.

Among the setting systems mentioned above, the systems of kappa-carrageenan with cation and gellan gum with cation are specifically preferred. They produce high gel strength at low concentrations and have excellent compatibility with HPS.

The amount of the hydrocolloid is preferably in the range of 0.01 to 5% by weight and especially preferred 0.03 to 1.0% in the aqueous HPS OR HES solution.

The cations are preferably selected from  $K^+$ ,  $Na^+$ ,  $Li^+$ ,  $NH_4^+$ ,  $Ca^{++}$  or  $Mg^{++}$ , for kappa-carrageenan is preferred  $K^+$ ,  $NH_4^+$  or  $Ca^{++}$ . The amount of cations is preferably less than 3%, especially 0.01 to 1% by weight in the aqueous HPS OR HES solution.

The preferred sequestering agents are ethylenediaminetetraacetic acid, acetic acid, boric acid, citric acid, edetic acid, gluconic acid, lactic acid, phosphoric acid, tartaric acid or salts thereof, methaphosphates, dihydroxyethylglycine, lecithin or beta cyclodextrin and combinations thereof. Especially preferred is ethylenediaminetetraacetic acid or salts thereof or citric acid or salts thereof. The amount is preferably less than 3%, especially 0.01 to 1% by weight of the dipping solution.

The inventive HPS OR HES compositions may contain in a further aspect additional pharmaceutically or food acceptable colouring agents in the range of from 0 to 10% based upon the weight of the film. The colouring agents may be selected from azo-, quinophthalone-, triphenylmethane-, xanthene- or indigoid dyes, iron oxides or hydroxides, titanium dioxide or natural dyes or mixtures thereof. Examples are patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D+C red 33, D+C red 22, D+C red 26, D+C red 28, D+C yellow 10, yellow 2 G, FD+C yellow 5, FD+C yellow 6, FD+C red 3, FD+C red 40, FD+C blue 1, FD+C blue 2, FD+C green 3, brilliant black BN, carbon black, iron oxide black, iron



oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, anthocyanines, turmeric, cochineal extract, chlorophyllin, canthaxanthin, caramel, or betanin.

The HPS OR HES capsules of the invention may be coated with a  
5 suitable coating agent like cellulose acetate phthalate, polyvinyl acetate phthalate, methacrylic acid gelatines, hypromellose phthalate, hydroxypropylmethyl cellulose phthalate, hydroxyalkyl methyl cellulose phthalates or mixtures thereof to provide e.g. enteric properties.

10 The HPS OR HES capsules of the invention may be used for the production of containers for providing unit dosage forms for example for agrochemicals, seeds, herbs, foodstuffs, dyestuffs, pharmaceuticals, flavouring agents and the like.

The HPS OR HES capsules of the invention may be used where a  
15 release of filled product must occur at low temperature, such as at room temperature, which is not achievable with gelatine capsules.

The following examples and tests demonstrate the HPS OR HES capsule production and properties:

20 **Example 1: Production of HPS capsules with 15% plasticizer**

1.5 kg of HPS powder is mixed with 25 g of kappa-carrageenan. To 3.21 kg of deionised water under stirring is added 0.5 g of potassium acetate (0.01% by weight in the solution) and 265 g of glycerol (5.3% in solution and 15% in capsule),  
25 followed by addition of the above mixture (30% of HPS and 0.5% of carrageenan in the solution). After the HPS is well dispersed, the dispersion is heated up to 90°C under slow

stirring, then held under strong stirring for 10 minutes to assure a good solubilisation of the components.

The HPS solution thus prepared is defoamed under slow stirring and then poured into a dipping dish of a pilot machine of conventional hard gelatine capsule production equipment. While keeping the dipping HPS solution at 60°C, natural transparent hard HPS capsules of size 0 were produced according to the conventional process with the same dimensional specifications to the conventional hard gelatine capsules.

Disintegration test results (according to USP XXIII 1995-<701> Disintegration):

First leak time: 21 seconds

Total disintegration time: 263 seconds.

**Example 2: Production of HPS capsules with 10% PVA and 10% plasticizer**

1.4 kg of HPS powder is mixed with 10 g of kappa-carrageenan and 175 g of PVA (PVA has a viscosity of 33 cps at 4% and 20°C). To 3.21 kg of deionised water under stirring is added 5 g of potassium acetate (0.10% by weight in the solution) and 175 g of glycerol (3.5% in solution and 10% in capsule), followed by addition of the above mixture (28% of HPS, 0.20% of carrageenan and 3.5% of PVA in solution). After the HPS is well dispersed, the dispersion is heated upto 90°C under slow stirring, then held under strong stirring for 30 minutes to assure a good solubilisation of the components.

The HPS solution thus prepared is defoamed under slow stirring and then poured into a dipping dish of a pilot machine of conventional hard gelatine capsule production equipment. While keeping the dipping HPS solution at 60°C, 5 natural transparent hard capsules of size 0 were produced according to the conventional process with the same dimensional specifications to the conventional hard gelatine capsules.

Disintegration test results:

10 First leak time: 51 seconds

Total disintegration time: 225 seconds

**Example 3: Production of HES capsules with 10% plasticizer**

1.30 kg of HES powder is mixed with 4.00 g of gellan. To 3.55 kg of deionised water under stirring is added 5.00 g of 15 potassium acetate (0.10% by weight in the solution), 2.00 g of ethylenediaminetetraacetic acid disodium salt (0.04%) and 145 g of glycerol (2.90% in solution and 10% in capsule), followed by addition of the above mixture (26.0% of HES and 0.08% of gellan in solution). After the HES is well 20 dispersed, the dispersion is heated upto 98°C under slow stirring, then held under strong stirring for 10 minutes to assure a good solubilisation of the components.

The HES solution thus prepared is defoamed under slow stirring and then poured into a dipping dish of a pilot 25 machine of conventional hard gelatine capsule production equipment. While keeping the dipping HES solution at 60°C, natural transparent hard capsules of size 0 were produced

WO 00/18835 PCT/US99/18139  
according to the conventional process with the same  
dimensional specifications to the conventional hard gelatine  
capsules.

Disintegration test results:

5 First leak time: 28 seconds

Total disintegration time: 443 seconds

We claim:

1. Film forming compositions consisting of modified  
starches, such as starch ethers or oxidized starch, more  
particularly hydroxypropylated starch or hydroxyethylated  
5 starch and a setting system.
2. Film forming compositions according to claim 1, wherein  
the setting system consists of hydrocolloids and cations.
3. Film forming compositions according to claim 1, wherein  
the setting system contains optionally sequestering  
10 agents.
4. Film forming compositions according to claim 1, wherein  
the content of hydroxypropylated starch is 88 to 98% by  
weight, of water is 2 to 12% by weight, of  
polysaccharides is 0.01 to 10%, preferably 0.05 to 5%by  
15 weight and of cation is 0.001 to 5%, preferably 0.01 to  
3% by weight.
5. Film forming compositions according to claim 1, wherein  
the hydrocolloids of the setting system are selected from  
polysaccharides.
- 20 6. Film forming compositions according to claim 1, wherein  
the hydrocolloids of the setting system are selected from  
alginates, agar gum, guar gum, locust bean gum (carob),  
carrageenan, tara gum, gum arabic, ghatti gum, Khaya  
grandifolia gum, tragacanth gum, karaya gum, pectin,  
25 arabian (araban), xanthan, gellan, starch, Konjac mannan,  
galactomannan, or funoran.

7. Film forming compositions according to claim 1, wherein the hydrocolloids of the setting system are selected from exocellular polysaccharides.
8. Film forming compositions according to claim 1, wherein the hydrocolloids of the setting system are selected from xanthan, acetan, gellan, welan, rhamsan, furcelleran, succinoglycan, scleroglycan, schizophyllan, tamarind gum, curdlan, pullulan, or dextran.
9. Film forming compositions according to claim 1, wherein the hydrocolloids of the setting system are selected from gellan gum or kappa-carrageenan.
10. Film forming compositions according to claim 1, wherein the optional sequestering agent or mixture of sequestering agents of the setting system is selected from ethylenediaminetetraacetic acid, acetic acid, boric acid, citric acid, edetic acid, gluconic acid, lactic acid, phosphoric acid, tartaric acid or salts thereof, methaphosphates, dihydroxyethylglycine, lecithin or beta cyclodextrin.
11. Film forming compositions according to claim 10, wherein the sequestering agent or mixture of sequestering agents is selected from ethylenediaminetetraacetic acid or salts thereof or citric acid or salts thereof.
12. Film forming compositions according to claim 1 containing additionally plasticizers in a range from about 0 to 40 % based upon the weight of the composition.
13. Film forming compositions according to claim 12 wherein the plasticizer or mixture of plasticizers is selected from polyethylene glycol, glycerol, sorbitol, sucrose, corn syrup, fructose, dioctyl-sodium sulfosuccinate,

triethyl citrate, tributyl citrate, 1,2-propylenglycol, mono-, di- or triacetates of glycerol, or natural gums.

14. Film forming compositions according to claim 1 containing additionally colouring agents in a range from about 0 to 5 10 % based upon the weight of the composition.
15. Film forming compositions according to claim 14 wherein the colouring agent or mixture of colouring agents is selected from azo-, quinophthalone-, triphenylmethane-, xanthene- or indigoid dyes, iron oxides or hydroxides, 10 titanium dioxide or natural dyes.
16. Film forming compositions according to claim 15 wherein the colouring agent or mixture of colouring agents is selected from patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D+C red 33, D+C red 15 22, D+C red 26, D+C red 28, D+C yellow 10, yellow 2 G, FD+C yellow 5, FD+C yellow 6, FD+C red 3, FD+C red 40, FD+C blue 1, FD+C blue 2, FD+C green 3, or brilliant black BN.
17. Film forming compositions according to claim 14 wherein 20 the colouring agent or mixture of colouring agents is selected from carbon black, iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, anthocyanines, turmeric, cochineal extract, chlorophyllin, canthaxanthin, caramel, or betanin.
- 25 18. Containers for unit dosage forms for agrochemicals, seeds, herbs, foodstuffs, dyestuffs, pharmaceuticals, or flavouring agents produced from the compositions according to claims 1 to 17.
- 30 19. Container according to claim 18 which is a pharmaceutical capsule.

20. Containers according to claim 18, characterised in that the container has a coating.
21. Coated containers according to claim 20 wherein the coating is selected from cellulose acetate phthalate, polyvinyl acetate phthalate, methacrylic acid gelatines, hypromellose phthalate, hydroxypropylmethyl cellulose phthalate hydroxyalkyl methyl cellulose phthalates or mixtures thereof.
22. Caplets encapsulated in film forming compositions according to claim 1.
23. Capsules according to claim 18 characterised in that the capsule halves are sealed with one or more layers of the composition according to claims 1 to 17.
24. Capsules according to claim 18 characterised in that a liquid fusion process seals the capsule halves.
25. Capsules according to claim 18 characterised by a release of filled product at low temperature, such as at room temperature.
26. Aqueous solutions of compositions according to claims 1 to 17 for the manufacturing of capsules.
27. Aqueous solutions according to claim 26, containing hydroxypropylated starch or hydroxyethylated starch in an amount of 10 to 60 %, preferably 20 to 40 % by weight, hydrocolloids in an amount of 0.01 to 5 %, preferably 0.03 to 1.0 % by weight and cations in an amount of 0.001 to 3 %, preferably 0.01 to 1 % by weight of the aqueous solution.



28. Aqueous solutions according to claim 26, containing optionally sequestering agents in an amount of 0.001 to 5 %, preferably 0.01 to 3 % by weight of the aqueous solution.
- 5 29. Use of aqueous solutions according to claim 26 for the manufacturing of hard capsules in a dip moulding process.
30. Manufacturing of hard capsules from aqueous hydroxypropylated starch solutions according to claims 26 to 28 in a dip moulding process with conventional hard  
10 gelatine capsules process parameters and equipment.

## INTERNATIONAL SEARCH REPORT

International Application No

F./US 99/18139

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C08L3/08 C08L3/18 C09D103/08 C08L3/10 C09D103/10  
 A61K9/48 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C09D C08L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 378 546 A (TOSHIO TSUZUKI ET AL.) 16 April 1968 (1968-04-16) column 2, line 54 - line 57 ---	1
A	DATABASE WPI Week 199307 Derwent Publications Ltd., London, GB; AN 1993-055171 XP002122906 "Soft capsule agent having controlled adhesivity during packaging etc. - has blended food fibre e.g. agar, carrageenan etc. in capsule film" & JP 05 004914 A (ASAHI KASEI KOGYO KK ET AL.), 14 January 1993 (1993-01-14) abstract --- -/--	1,6-10, 19,20, 23,27,28

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

17 November 1999

Date of mailing of the international search report

26/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040. Tx. 31 651 epo nl.  
 Fax: (+31-70) 340-3016

Authorized officer

Mazet, J-F

## INTERNATIONAL SEARCH REPORT

International Application No

F.../US 99/18139

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 026 986 A (CHRISTEN ET AL.) 31 May 1977 (1977-05-31) cited in the application the whole document ---	1, 19, 27, 30, 31
A	US 5 224 989 A (LIKAROVA) 6 July 1993 (1993-07-06)  abstract claims ---	1, 3, 11-19, 23, 27-29
A	EP 0 606 486 A (TEIJIN LIMITED) 20 July 1994 (1994-07-20) abstract -----	1, 2, 6, 7, 19, 23, 27

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

F.../US 99/18139

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3378546 A	16-04-1968	NONE	
JP 5004914 A	14-01-1993	NONE	
US 4026986 A	31-05-1977	NONE	
US 5224989 A	06-07-1993	NONE	
EP 606486 A	20-07-1994	AU 660824 B	06-07-1995
		AU 4355593 A	04-01-1994
		US 5626871 A	06-05-1997
		AU 659328 B	11-05-1995
		AU 4355693 A	04-01-1994
		CA 2115065 A	23-12-1993
		CA 2115444 A	23-12-1993
		EP 0611567 A	24-08-1994
		WO 9325193 A	23-12-1993
		WO 9325198 A	23-12-1993
		JP 2907551 B	21-06-1999